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Solidification techniques and dosage form development of solid self-emulsifying drug delivery systems: a technical note

Panner Selvam R, P.K. Kulkarni and Mudit Dixit

Department of Pharmaceutics, J.S.S College of pharmacy, J.S.S University, Mysore-570015, Karnataka, India.

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ABSTRACT

Oral drug delivery systems being the most economy and leads the worldwide drug delivery market. The major drawback in oral drug formulations is low and varying bioavailability, which mainly results from poor aqueous solubility. It is estimated that 40% of active substances are poorly water soluble. Among the various available approaches to improve the oral bioavailability of these molecules, the use of self-emulsified drug delivery systems (SEDDS) has been shown to be reasonably successful in improving the oral bioavailability. However, traditional preparations of SEDDS are usually prepared in the liquid state which produces some disadvantages, such as high production costs, low drug incompatibility and stability, drugs leakage and precipitation. To overcome this problem solid SEDDS (S-SEDDS), prepared by solidification of liquid/semisolid selfemulsifying (SE) ingredients into powders, have gained popularity. The S-SEDDS not only increase the solubility of the drug, but also exhibits the advantages of solid dosage form. The present review explains the recent trends in Solid SEDDS (S-SEDDS) with regard to the selection of lipid systems for current formulations, solidification techniques and the development of solid SE (self-emulsifying) dosage forms and their related problems and possible future research directions.

Introduction

Developing novel drug formulations to improve solubility and bioavailability is a challenge facing the pharmaceutical industry[1]. As a matter of fact, in the U.S. Pharmacopoeia, more than one-third of the drugs listed belongs to the poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that poor biopharmaceutical properties leads to more than 41% of the failures in new drug development, including water insolubility, while it was still indicated recently that about 50% failure of drug candidates was due to poor "drug-like" properties. In the pharmaceutical industry, it is commonly recognized that on average more than 40% of newly discovered drug candidates are poorly water-soluble [2]. The selection of an appropriate dosage form is critical because a dosage form with poor drug delivery can make a useful drug worthless [3].

Lipid formulations are a diverse group of formulations consisting of mixture of excipients such as triglycerides, mixed glycerides, lipophilic surfactants, hydrophilic surfactants and cosolvents[4].

SEDDS (Self Emulsifying Drug Delivery System) are solid dosage form with a unique property, that is they are able to self emulsify rapidly into fine O/W emulsion in the gastrointestinal fluids, under gentle agitation provided by the gastrointestinal tract. This fine O/W emulsion results in small droplets of oil dispersed in the gastrointestinal fluids that provide a large interfacial area enhancing the activity and minimizing the irritation due to contact of drug in the gut wall[5].

The lipidic excipients reportedly alter GI motility, increase bile and mesenteric lymph flow and possibly reverse the influence of P-glycoprotein. Further, lipid-based formulations can decrease the intrinsic limitations of slow and incomplete dissolution of poorly water soluble drugs by facilitating the formation of solubilised phases from which absorption takes place[6]. Additional advantages are Selective targeting of drug(s) toward specific absorption window in GIT, Protection of sensitive drug substances and thermodynamically stable when compared to the simple emulsions[7, 8].

Widening availability of lipidic excipients with specific characteristics offer flexibility of application with respect to improving the bioavailability of poorly water-soluble drugs and manipulating their release profiles[9].

However, traditional preparations of SEDDS are usually prepared in the liquid state. So the liquid SEDDS are generally enclosed by soft or hard capsules to facilitate oral administration but it produce some disadvantages, such as high production costs, low drug incompatibility and stability, drugs leakage and precipitation, capsule ageing. Then incorporation of liquid SEDDS into a solid dosage form is compelling and desirable, and some solid self-emulsifying (SE) dosage forms have been initially explored, such as SE tablet and pellets[5, 10].

Solidification Techniques

Capsule filling with liquid and semisolid self-emulsifying formulations

The self emulsifying formulations mostly will be in liquid or semisolid form due to the presence of large amount of lipids. Capsule filling is the one of the most economical and common techniques for the encapsulation of liquid or semisolid self emulsifying formulations for the oral route.

For semisolid formulations, it is a four-step process

(i) Heating of the semisolid excipients to at least 20°C above its melting point.

(ii) Incorporation of the active substances.

(iii) Capsule filling with the molten mixture and

(iv) Cooling to room temperature.

For liquid formulations, it involves a two-step process Filling of the formulation into the capsules followed by sealing

Tele: +919844795544
E-mail addresses: selva.r9@gmail.com

of the body and cap of the capsule, either by banding or by micro spray sealing.

Advantages

- simplicity of manufacturing;
- suitability for low-dose highly potent drugs and
- high drug loading potential (up to 50% (w/w)[5,11].

Spray drying

In this technique, formulation preparation involves by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixtures before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The volatile phase (e.g. the water contained in an emulsion) evaporates as the droplets introduced into a drying chamber, forming dry particles under controlled temperature and airflow conditions[12].

Critical parameters of spray drying includes Inlet temperature of air, Outlet temperature of air, Viscosity, Solid content, Surface tension, Feed temperature, Volatility of solvent, Nozzle material. . According to the drying characteristics of the product and powder specification the atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected[13].

Advantages

- Able to operate in applications that ranges from aseptic pharmaceutical processing to ceramic powder production.
- It can be designed to virtually any capacity required
- Spray drying process is very rapid.
- Adaptable to fully automated control system that allows continuous monitoring and recording of very large number of process variables simultaneously.
- Availabe in wide designs to meet various product specifications.
- It has few moving parts and careful selection of various components can result in a system having no moving parts in direct contact with the product, thereby reducing corrosion problems.
- It can be used with both heat-resistant and heat sensitive products.
- As long as they are can be pumped, the feedstock can be in solution, slurry, paste, gel, suspension or melt form.
- Offers high precision control over Particle size, Bulk density, Degree of crystallinity, organic volatile impurities and residual solvents.
- Powder quality remains constant during the entire run of the dryer. Nearly spherical particles can be produced, uniform in size and frequently hollow, thus reducing the bulk density of the product.

Disadvantages

- The equipment is very bulky and with the ancillary equipment is expensive.
- The overall thermal efficiency is low, as the large volumes of heated air pass through the chamber without contacting a particle, thus not contributing directly to the drying[12-15].

Spray congealing

It also referred to as spray cooling, the process involves spraying molten formula into a cooling chamber and, upon contact with the cooling air, the molten droplets congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber as fine powder. The fine powder may then be used for development of solid dosage forms such as tablets or capsules. Equipment like rotary, pressure, two-fluid or ultrasonic atomizers are available to atomize the liquid mixture and to generate droplets. Most of the recent research conducted on spray cooling with lipid-based excipients used ultrasonic atomizers. The main classs of excipient used with this technique are polyoxylglycerides and, more specifically, stearoyl polyoxylglycerides Gelucire® 50/13 [16].

The congealed particles are strong and nonporous as there is an absence of solvent evaporation. Ideally, the meltable materials should have defined melting points or narrow melting ranges[17].

Advantages

- Spray Cooling Operation is continuous and easy, operation is adaptable to fully automatic control, and response times are fast.
- The specification or powder quality remains constant throughout the entire cooling operation irrespective of the time when cooling conditions are held constant.
- Feedstock in melt form can be handled is pumpable whether they be corrosive, abrasive or not.
- Spray Coolers are available in wide range of designs and layouts

Disadvantages

- High installation costs.
- Industrial units are physically larger per unit output than other methods of obtaining powders. This makes Spray Coolers expensive to fabricate[18].

Solid carriers

In this technique the adsorbents (free flowing powder material) having good adsorption efficiency were used to adsorb the liquid self emulsifying formulations on to it and converted into solid form. This procedure involves two steps

- The mixture is uniformly adsorbed by mixing in a blender.
- The obtained solid mixture is directly filled into capsules or by adding suitable excipients compressed into tablets[5].

Solid carriers can be microporous inorganic substances, highsurface- area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for example, silica, silicates, microporous calcium silicate (FloriteTM RE); magnesium aluminum silicate (NeusilinTMUS2) and silicon dioxide (SylysiaTM 320). magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and crosslinked polymethyl methacrylate .Cross-linked polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation .Nanoparticle adsorbents comprise porous silicon dioxide (Sylysia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal[19,20] .

Melt granulation

Melt granulation is a single step-process allowing the converting granules from a powder mix (containing the drug). The technique requires high shear mixing in presence of a meltable binder (Polyoxylglycerides, lecithin, partial glycerides etc) which may be sprayed in molten state onto the powder mix as in classic wet granulation process. In this technique the binder (solid or semi-solid) may be blended with the powder mix, the heat generated from the friction of particles during high shear mixing forms liquid bridges with the powder particles that shape into small granules.

Formulation parameters to consider are:

i) Drug particle size, shape, and its solubility in the binder;
ii) Binder concentration.
iii) The melting point and thermoplastic behavior of the binder

Typically, lipid-based binders are used between 15% and 25% w/w level depending on the fineness of the powder mixture. Generally, lipids with low HLB and high melting point are suitable for sustained release applications. Semi-solid excipients with high HLB on the other hand may serve in immediate release and bioavailability enhancement[21].

Advantages

- Neither solvent nor water used in this process.
- Fewer processing steps needed thus time consuming drying steps eliminated.
- There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non-swellable and water insoluble nature.

Disadvantages

- Requires high energy input.
- The melt technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
- Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates
- Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials[22, 23, 24].

Melt extrusion/extrusion spheronization

Melt extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions[25]. Pharmaceutical products manufactured using melt extrusion techniques have been approved in the USA, Europe and Asia. In pharmaceuticals, melt extrusion technique is used to disperse an active ingredient(exhibit thermal stability) in a thermal carrier material. The carrier substance is usually a polymer or low melting point wax. Heat generated due to friction by the screw is sufficient to melt wax. The physical and chemical properties of the carriers have significant effect on the drug release characteristics[26].

The extrusion–spheronization process requires the following steps:

- Dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder.
- Extrusion into a spaghetti-like extrudate.
- Spheronization from the extrudate to spheroids of uniform size.
- Drying Sifting to achieve the desired size distribution and coating (optional)[27].

The main monitoring and controlling parameters are barrel temperatures, feed rate, screw speed, motor load and melt pressure, viscosity and variation of viscosity with shear rate and temperature[28].

Advantages

- Small equipment
- Economic continuous process and scale up flexibility
- Solvent- free manufacture
- High mixing efficiency
- Closed process unit to prevent cross contamination
- Short processing time
- Easily controlled process parameters
- Possibility of online analytics for process control

Disadvantages

- Thermal process (drug/polymer stability)
- Flow properties of the polymer are essential to processing
- Limited number of available polymers
- Requires high energy input.
- The melt technique is that the process cannot be applied to heat sensitive materials owing to the elevated temperatures involved[29, 30].

Supercritical fluid based methods

This method uses lipids in supercritical fluid based methods for coating of drug particles, or for producing solid dispersions. The process for obtaining solid particles involves dissolving the drug and lipid-based excipient(s) in an organic solvent such as methanol and then in a supercritical fluid, followed by lowering the temperature and pressure conditions to reduce their solubility in the fluid. The important considerations with this formulation technique are

i) The solubility of the active substance and excipients in the supercritical fluid.

ii) The integrity/ stability of the active substance under the process conditions, and

iii) The energy or environmental concerns relating to the evaporation of solvents if applicable. Supercritical fluid based methods is best suited for highly potent, low-dose drugs due to its highest potentials for lipid exposure and a relatively lower drug loading capacity. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water[31, 32].

Basic techniques in SCF technology

- Rapid Expansion of Supercritical Solutions
- Gas Antisolvent Recrystallisation
- Precipitation with Compressed Fluid Antisolvent
- Impregnation or infusion of polymers with bioactive materials
- Solution enhanced Dispersion by Supercritical Fluid[33].

The selection of formulation techniques for bioavailability enhancement with lipid-based excipients is given in Table I. It also explains the formulation advantages and its limits

Dosage Forms of S-Sedds

Self-emulsifying solid dispersions

Despite many advantages of solid dispersion, drawbacks related to preparation, reproducibility, formulation, scale up, and stability minimizes its use in commercial dosage forms for poorly water-soluble drugs. In recent years, due to the availability of surface-active and self-emulsifying carriers with relatively low melting points, successful developments of solid dispersion systems for preclinical, clinical and commercial use have been feasible. The dosage form preparation involves, dissolving of drugs in melted carriers and the filling of the hot solutions into gelatin capsules. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and as expected to change significantly during the scale up [34].

Self-emulsifying sustained/controlled-release pellets

As a multiple-unit dosage form, pellets have some desired advantages, Pellets disperse readily in the gastrointestinal tract and thus improves absorption of drug, reduce peak plasma fluctuations, and minimize side effects, high local concentrations of drug are avoided such as flexibility in designing and developing solid dosage form, reduction of intra- and inter-subject variability of drug dissolution and plasma profiles, hence

improvement of the drug safety and efficacy, different drug substances (e.g. incompatible drugs) can be formulated and blended into a single dosage form[35].

E. Franceschinis et al. prepared self-emulsifying pellets by wet granulation of powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and di-glycerides, polisorbate 80 and water, in a 10-l Roto-J Zanchetta high shear mixer. has been investigated. The data demonstrate that pellets composed of oil to surfactant ratio of 1:4 (w/w) presented improvement in performance in permeation experiments[36]

Z. Wang et al prepared nitrendipine (NTD) self-emulsifying (SE) pellets via extrusion/spheronization technique, using liquid SEDDS (NTD, Miglyol® 812, Cremophor® RH 40, Tween 80, and Transcutol® P), adsorbents (silicon dioxide and crospovidone), microcrystalline cellulose and lactose. AUC of NTD from the SE pellets showed 1.6-fold greater than the conventional tablets and no significant difference compared with the liquid SEDDS. In conclusion, the studies illustrated that extrusion/spheronization technique could be a useful large-scale producing method to prepare the solid SE pellets from liquid SEDDS, which can improve oral absorption of NTD, nearly equivalent to the liquid SEDDS, but better in the formulation stability, drugs leakage and precipitation, etc[10].

Ahmed Abdalla et al., prepared solid self-emulsifying pellets by extrusion/spheronization technique. Spherical pellets were made from a mixture of C18 partial glycerides, Solutol HS15 and microcrystalline cellulose. The pellets were, in contrast to pellets lacking Solutol, able to transfer a lipophilic dye and a spin probe into the aqueous media. Furthermore, the prepared formulation was capable of accelerating the release of the drug diazepam and maintaining its concentration above its saturation solubility[37].

Dry emulsions

Dry emulsions are fine powders, which forms fine emulsion on contact with aqueous fluid invivo. These fine powders can be filled directly into capsule or punched into tablet for better patient compliance. Dry emulsion formulations are generally prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin etc) in the aqueous phase by rotary evaporation, freeze-drying or spray drying[38, 39].

Balakrishnan et al., prepared solid SEDDS(dry emulsion) of dexibuprofen, by spray drying liquid SEDDS with an inert solid carrier Aerosil 200. The liquid SEDDS was prepared by dexibuprofen, Labrasol, Capryol 90 and Labrafil M 1944 CS. The solid SEDDS gave significantly higher AUC and Cmax than did dexibuprofen powder ($P < 0.05$). In particular, the AUC of solid SEDDS was about twofold higher than that of dexibuprofen powder[40].

Self-emulsifying beads

Patil P et al., formulated loratadine self-emulsifying system (SES) and explored the potential of porous polystyrene beads (PPB) as carriers for such SES. Isotropic SES was formulated, which comprised Captex 200 , Cremophore EL, Capmul MCM . In vitro drug release was rapid in case of SS beads due to the presence of SES near to surface. Geometrical features such as bead size and pore architecture of PPB were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB [41].

Self-nanoemulsifying granules

R.P. Dixit et al., prepared free flowing Self-nanoemulsifying granules (SNGs) of the ezetimibe using varying proportions of hydrophilic colloidal silicon dioxide as an adsorbing agent. Dissolution studies revealed remarkable increase in dissolution of the drug as compared to plain drug. In vivo evaluation in rats showed significant decrease in the total cholesterol levels as compared to positive control. The SNGs filled into hard gelatin capsules showed two to threefold increase in the dissolution rate as compared to plain drug filled capsules signifying its potential in improved delivery of lipophilic drugs. Ezetimibe was conveniently formulated in emulsion and converted to SNG with colloidal silicon dioxide[42].

Self-emulsifying capsules

SEDDS are normally prepared as liquid dosage forms that can be administrated in soft gelatin capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/spheronization to provide a good in vitro drug release (100% within 30 min, T50% at 13 min)[43].

Kaseem AA et al., prepared self-nanoemulsified drug delivery system (SNEDDS) for clotrimazole (CT), used in vaginal delivery.. Based on solubility studies, oil phase (oleic acid without or with coconut oil), surfactant (Tween 20), and co-surfactants (PEG 200 and n-butanol) were selected. In vitro release studies were performed with SNEDDS formulations in capsules, and the plain drug served as a control. Results suggested that the prepared SNEDDS formulations produced acceptable properties in terms of immediate drug release and could increase the bioavailability of CT [44]

Self-emulsifying sustained/controlled-release tablets

Wei L et al., prepared Self-emulsifying osmotic pump tablet (SEOPT) of Carvedilol using Gelucire 44/14, Lutrol F68, Transcutol P, silicon dioxide, mannitol, citric acid, and sodium hydrogen carbonate. The results showed that the shape of the resultant emulsion was round and uniform. Self emulsifying system improves the solubility of carvedilol, hence it guarantee a complete release of carvedilol under the osmotic pressure of mannitol. The plasma concentrations were more stable compared with that of commercially available tablet[45]

Self-emulsifying sustained-release microspheres

Zvonar A et al., improved the solubility and permeability of furosemide by formulating as Ca-pectinate microcapsules with self-microemulsifying core. By using an Inotech IE-50R encapsulator, equipped with a concentric nozzle was utilized to transform liquid self-microemulsifying system (SMES) to solid microcapsules. The obtained results illustrate the prospective use of microcapsules with self-microemulsifying core for the delivery of compounds with poor biopharmaceutical properties via the oral route[46] You J et al., prepared sustained-release microspheres with self-emulsifying capability containing zedoary turmeric oil (ZTO) by quasi-emulsion-solvent-diffusion method. The bioavailability of the microspheres and conventional ZTO self-emulsifying formulations for oral administration was compared using rabbits. The improved sustained-release characteristics were achieved after oral administration of the microspheres with a improved bioavailability with respect to the conventional self-emulsifying [47].

Self-emulsifying nanoparticles

Many nanoparticle techniques have been useful in the formulation of self-emulsifying nanoparticles. Solvent injection

is one of the widely used techniques. The method involves melting the lipid, surfactant, and drugs together, and injected drop wise into a stirred non-solvent. The obtained self-emulsifying nanoparticles were filtered out and dried. This approach yields nanoparticles (about 100 nm) with a high drug loading efficiency of 74%[48].

W. J. Trickler et al., developed paclitaxel (PTX) nanoparticle drug delivery system using chitosan and glyceryl monooleate (GMO). The solubility of PTX enhanced by SE property of GMO and provided a foundation for chitosan aggregation, meanwhile causing complete loading and entrapment of PTX. These improves the bioavailability and less use of the drug for the action, thereby reduces the adverse effects[49].

Self-emulsifying suppositories

Gugulothu D et al., formulated self-microemulsifying suppositories of β-artemether with faster onset of action and prolonged effect to be administered by rectal route. The developed self-microemulsifying suppositories could sustain the activity (94%) for 20 days post infection. The survival of animals was also better as compared to the conventional formulation[50]

Self-emulsifying implants

Chae GS et al., prepared 1, 3-bis(2-chloroethyl)-1-nitrosourea (BCNU) SEDDS for improvement of stability. The self-emulsified (SE) BCNU was loaded into PLGA wafer as a new polymeric implant. In vitro release of BCNU was prolonged up to 7 days from SE BCNU-loaded PLGA wafer and it followed first order release kinetics. The final result depicts SE BCNU degraded much more slowly than the intact BCNU in PLGA matrix at 25°C[51].

Conclusion

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. SEDDS enhances the bioavailability of the poorly soluble drugs by improving both solubility as well as permeability. Tradional form of SEDDS ie liquid, has many drawbacks like poor patience compliance, increased production cost etc. Currenly different solidification techniques are available, by which the final dosage form can be prepared as solid form. Depending on the drug, excipients and the release rate required, suitable solidification technique were selected. Selection of excipients is the most important in the preparation of Solid SEDDS. The properties of the currently available excipients should be thoroughly exploited for the proper use of the excipients. Already drugs like Cyclosporine A, Ritonavir, and Saquinavir, which are, available on the market as self emulsifying formulations. By increasing the excipients range and data available for the preparation techniques and optimisation , can expect more number of drugs in the form of solid SEDDS in future.

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Table I: Considerations in selection of formulation techniques for bioavailability enhancement with lipid-based excipients.

Formulation techniques for solid and semi-solid formulations	Physical property of the lipid excipients applied		Formulations advantages and limits	
	Liquid to solid	Semi-solid	Maximum lipid exposure* (%, w/w)	Maximum drug Loading (%, w/w)
Capsule filling	X	X	99	50
Spray-cooling	X		99	30
Spray drying	X	X	60	50
Adsorption on solid carrier	X		80	10
Melt granulation	X		50	80
Melt extrusion	X		50	60
Super critical fluid based methods	X		99	20